REMARKS/ARGUMENTS

This supplements the Second Amendment After Final concurrently filed herewith. Applicants note with appreciation the courtesies extended to Applicants' undersigned representative in a telephone interview. As discussed during the telephone interview, the claimed invention is directed to water soluble particles which include a coprecipitant core with a dehydrated biological macromolecule coated thereon, wherein said coprecipitant has a molecular weight of less than 1,000 Da. In contrast, Randen et al. cited by the Examiner is directed to particles in which the coprecipitant and enzyme are intermingled. Applicants offer the following comments to supplement prior arguments and further demonstrate the differences between the claimed invention and the cited art.

The present inventors conducted a study to establish the differences between particles formed using the process described in the present invention and particles formed using the Randen et al. method. The inventors also considered particles formed using the Bustos et al. method. Bustos et al. was cited by Applicants in the Information Disclosure Statement filed January 28, 2002. As noted in Applicants' response filed April 16, 2003, Bustos et al. refer to the Randen et al. paper.

As a preliminary matter, as also previously noted by Applicants, the process description in Randen et al. is ambiguous and does not specify the order of addition of solvent and aqueous solution. As is typical for other procedures, Applicants submit that the skilled artisan would generally add the solvent to the aqueous phase. This is supported by Bustos et al., which refers to the Randen paper and specifically adds the solvent to the aqueous solution, which is opposite from that of the present invention. Thus Applicants submit that the skilled artisan, upon reading Randen et al., would add the solvent to the aqueous solution. This is a fundamental difference from the process of the present invention.

Particles prepared by the inventors in accordance to the Randen et al. and Bustos et al. process were evaluated by differential scanning calorimetry (DSC). The DSC results demonstrate that sharp melting peaks are obtained for the particles of the present invention whereas the starch samples (i.e. as disclosed in Randen et al., prepared by adding the solvent to the aqueous solution) do not. This indicates that large molecules, such as starch, produce

particles which are likely to possess amorphous cores in which the biomolecule is distributed throughout. In contrast, in the claimed invention, the co-precipitant with a molecular weight of less than 1,000 Da (for example, as recited in claim 1) rapidly forms crystals of high lattice energy which prevent inclusion of biomolecules within the interior and on co-precipitation are found to give rise to micro-particles coated with biomolecules.

Biomolecule coated particles have advantageous properties compared to those in which the protein is included and distributed throughout (i.e. as found in Randen et al. on page 765, right-hand column, 4th paragraph from the bottom and the sentence starting "The use of...."). For example, biomolecule coated particles have very high local concentration on the particle surface and are freely available for reaction with reactants such as substrates, inhibitors, drugs, cross-linkers, solubility modifiers, bio-activity modifiers (e.g. PEG), etc.

Furthermore, small molecules such as those with a molecular weight of less than 1,000 Da have the advantage that they are able to crystallize very rapidly and at low temperatures and so micro-crystals can be produced during the rapid co-precipitation process.

Particles with a crystalline core have many advantageous properties compared to those with an amorphous core. For example, biomolecules coated onto a molecularly flat crystalline surface, as obtained on coprecipitation, can be directly imaged using scanning probe microscopy techniques. This can provide information about protein shape, orientation at surfaces and complexes formed prior to precipitation. Furthermore, protein coated microcrystals can be used to efficiently form biomolecular imprints by polymerization of functional monomers around microcrystals suspended in an organic solvent because the biomolecules are concentrated at the surface. On amorphous surfaces the surface concentration of biomolecules will be too low to be useful.

Large molecules and polymers such as starch are generally very slow to crystallize (except by cooling from a melt) and produce particles with mainly amorphous cores on co-precipitation. Claim 2 currently refers to the crystalline nature of the core.

The inventors also evaluated the particles by scanning electron micrograph (SEM). Attached is a copy of an image of starch particles obtained by the inventors when they repeated

the process of Randen et al. (i.e. adding the solvent to the aqueous solution). These are clearly not crystalline and, as shown by the slide bar, are much larger than 50 microns.

A number of additional advantageous features of the claimed invention are set forth below.

(i) **The production of particles less than 50 microns in a single process step.**

The process described in the present invention has considerable industrial advantages in terms of ease of manufacture. The process is quicker and cheaper and has been demonstrated to leave a significant proportion of the biomolecule in a native conformation, on the surface of particles less than 50 microns.

In contrast, the process used in Randen et al. produces particles much larger than 50 microns. Such particles would need further time intensive processes such as milling and sieving to bring them into the claimed size range. Such processes have been demonstrated to be inefficient using conventional equipment (see Randen et al.) and if intensified are likely to lead to damage of the biomolecule. Damaged biomolecules can lead to an undesirable and potentially dangerous immunological response if used in a pharmaceutical formulation

(ii) **The production of discrete well-defined regular particles less than 50 microns with a narrow size range.**

The present invention also has the advantage that the particles are easier to process into suspensions, coatings and can be used to make free-flowing powders well suited for pharmaceutical formulations such as for pulmonary and parenteral applications. This comes from the discrete well-defined regular particle sizes less than 50 microns.

In contrast, in the prior art such as Randen et al., starch particles much larger than 50 microns are produced. Following milling, they are reported to be still mainly larger than 50 microns, irregular in shape and show a wide size distribution (see Randen et al. at page 764, Table 3). Having a wide size distribution and shape makes it difficult to obtain suitable conditions for further process steps. For example, the smallest and largest fractions will have

very different settling properties. The particles are also reported to not be free flowing and are therefore not well suited for making pharmaceutical formulations where precise dosing into vials or other delivery devices is generally required.

(iii) **The production of particles in which the core material can straightforwardly be separated from the biomolecules by dialysis, ultrafiltration etc.**

Particles, in general, may have to be stored and/or shipped wherein the particles may disintegrate and/or degrade.

The biomolecules in the present invention may be advantageously stored and shipped as dry powders. However, prior to application the biomolecules may need to be purified from the co-precipitant. This is much more efficiently achieved with low molecular weight compounds (i.e. less than 1,000 Da). The biomolecules are therefore, if necessary, easy to separate in the present invention.

In contrast, separation by dialysis or ultrafiltration relies on differences in molecular size and will be inefficient or ineffective for large molecules such as starch (i.e. Randen et al.).

(iv) **Production of particles that dissolve very rapidly on exposure to water.**

The present invention advantageously produces small hydrophilic particles which tend to become fully solvated and disperse more quickly than large hydrophilic molecules. This has advantages for the reconstitution of pharmaceutical formulations because it is desirable that redissolution of protein occurs rapidly but with minimum agitation. It is important to appreciate that this is only possible because the particles are water soluble themselves.

Supplemental Information Disclosure Statement

Also filed concurrently herewith is a supplemental Information Disclosure Statement, presenting GB 2,131,948A for consideration by the Examiner. As discussed above, the claimed invention is directed to water-soluble particles comprising a coprecipitant core with a dehydrated

biological macromolecule coated thereon, wherein said coprecipitant has a molecular weight of less than 1,000 Da. GB 2,131,948A relates to proteins adsorbed to the surface of polymeric beads. In contrast to the claimed invention, however, the particles of GB 2,131,948A are not water-soluble. GB 2,131,948A reports that the beads are prepared and used in an aqueous suspension. See page 2, lines 24 to 27. Thus the particles of GB 2,131,948A would not be considered to have water-soluble cores. Furthermore, the polymers used in GB 2,131,948A such as cross-linked polyacrylamide will have molecular weights greater than 1,000 Da as claimed. Accordingly, the claimed particles differ from the particles of GB 2,131,948 A.

Conclusion

In summary, the cited art does not teach or suggest water soluble particles comprising a coprecipitant core with a dehydrated biological macromolecule coated thereon. Further the cited art does not teach or suggest the use of a coprecipitant with a molecular weight less than 1,000 Da. Accordingly Applicants respectfully submits that the claimed invention is novel and nonobvious and request withdrawal of the rejections of record.

The rejections of record having been addressed above in full, Applicants respectfully submit that the claimed invention is in condition for allowance, which action is respectfully solicited. Should the Examiner have any questions regarding the foregoing, it is respectfully requested that the Examiner contact the undersigned at her convenience.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required

therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

Melissa B. Pendleton
Registration No. 35,459

Customer No. 00826
ALSTON & BIRD LLP
Bank of America Plaza
101 South Tryon Street, Suite 4000
Charlotte, NC 28280-4000
Tel Charlotte Office (704) 444-1000
Fax Charlotte Office (704) 444-1111
CLT01/4621708v1

CERTIFICATION OF FACSIMILE TRANSMISSION

I hereby certify that this paper is being facsimile transmitted to the US Patent and Trademark Office at Fax No. 703-872-9306 on the date shown below.

Grace R. Rippy

December 1, 2003
Date

SC/PES100/2PrOH
(Sample 1)
according to Randen et al (pouring),
6.25% loading, PES100 in H2O =15%
MKB1x1a

SC/PES100/2PrOH
(Sample 1)
according to Randen et al (pouring),
6.25% loading, PES100 in H2O =15%
MKB1x4a